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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,010	12/30/2003	Randolph J. Noelle	58281US004	7654

32692 7590 09/15/2006

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 09/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,010	NOELLE ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *6,7,11-48,50-52 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-10,49,53 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-57* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date
ul :1/23/06,11/26/04,9/2/04,4/21/05, 11/2/04.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on June 29, 2006, is acknowledged. Election of species TLR7 agonist as the TLR agonist, CD40 as the TNF/R agonist, and tumor antigen as the antigen is also acknowledged, reading on claims 1-5, 8-10, 49, 53 and 55-57.

Claim Objections

Claims 1-5, 8-10, 49 and 55-57 are objected to for comprising non-elected species.

Claim 1 is objected to for failing to define the first occurrence of the acronym "TLR" and TNF/R" in the claims. Claim 3 is objected to for failing to define the first occurrence of the acronym "IRM" in the claims. Applicant may wish to consider amending the claims to read --- Toll-Like Receptor (TLR)-- and "Tumor Necrosis Family or Tumor Necrosis Family Receptor (TNF/R)-- at line 2 of claim 1, and --an immune response modifier (IRM)--- at line 2 of claim 3 for clarity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8-10, 49, 53 and 55-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a known TLR7 agonist, such as an IRM compound comprising an imidazoquinoline amine, *e.g.*, imiquimod and R-848 (resiquimod), and for a known CD40 agonist comprising the receptor binding domain of CD40 ligand or an α-CD40 agonist antibody, does not reasonably provide enablement for the broad genus of TLR agonists or of TNF/R agonists, including unknown agonists of TLR7 (such as its natural ligand) or of CD40. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-5 and 8-10 are drawn to an immunostimulatory combination comprising a TLR agonist and a TNF/R agonist, when in combination are effective to increase a subject's immune response to an antigen. It is noted that though both agonists must be present, only one needs to be effective in immune response stimulation. It is only necessary that when in combination they are effective. There is no requirement, for example, for a synergistic effect.

Claims 49, 53 and 55-57 are drawn to a vaccine comprising a TLR agonist, TNF/R agonist and an antigen, which when combined are effective for inducing an immune response to the antigen in a subject immunized with the vaccine. As with the earlier claims, there is no requirement of synergistic action, only that an immune response be elicited. Unless the antigen is human, and even in some cases when it is human, it highly likely that an immune response will result upon vaccination with the antigen. There is no limitation about the extent of the response, which means that while the presence of the agonists is required, an effect of the agonists is not.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The natural ligand(s) of TLR7 as well as other TLRs is unknown, though they, like the ligands of other TLRs have been much sought after (*e.g.*, Jurk et al., #C8, filed by Applicants 11/26/04, end of first paragraph of col. 2). Because TLRs are involved in the body's reaction to bacteria, viruses and parasites, they are recognized as important to the body's natural immune response. The diversity of ligands they bind is unknown, even though each receptor had at least several identified ligands by the effective filing date of the instant application. However, as late as August 2001, Akira et al. (#C8, filed by Applicants 11/26/04, p. 679, col. 2, first full paragraph) reported that, "The past two years have seen rapid progress in our understanding of how TLRs function in recognition of pathogens. Ligands of TLR2, TLR4, TLR5, TLR6 and TLR9 have been identified, but the identity of ligands recognized by the other TLRs remain unknown." Akira et al. go on to caution that overexpression studies can be misleading and, while the use of knockout mice is the best way to identify natural ligands, potential artifacts are a

concern. "How the TLRs recognize their ligands is still unknown. A unique characteristic of ligand recognition by TLRs is that it is specific yet diverse.... Because high-affinity ligand binding to a TLR has not been shown, it is possible that unknown coreceptors may be required for specific recognition of each ligand. Crystal structure studies will be necessary to elucidate the interaction between the particular TLR and its ligand." (p. 679, col. 2, third full paragraph). Akira et al. highlight the problems associated with TRL ligand identification.

A TNF/R agonist can, like some of the TLR agonists, affect more than one receptor or ligand. This is so because the TNF ligand superfamily and TNF receptor superfamily are large and complex. Pathways may be distinct, redundant or interacting. (*e.g.*, Fitzgerald et al., The Cytokine Facts Book, 2nd Ed., 2001) Also, while many TNF/R agonists have been identified, some necessarily remain unknown.

For these reasons, the specification is not considered enabling for one of skill in the art to make and use the claimed invention commensurate in scope with the claims because the amount of experimentation required is undue, the claims are of very broad scope, there is a lack of working examples and guidance provided in the specification to support the scope of the claims and a high degree of unpredictability as evidenced by the prior art, so that attempting to construct and test every possible compound for its ability to be an agonist of a TLR, *e.g.*, of TLR7, or of a TNF/R, *e.g.*, of CD40, would constitute undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8-10, 49, 53 and 57-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ito et al. (J. Exp. Med. 195:1507, 2002), Hemmi et al. (#C6, filed by Applicants 9/2/04) and Melief et al. (Immunol. Rev. 188:177, 2002).

Ito et al. teach TLR7 imidazoquinoline ligands, imiquimod and resiquimod (R-848), induce production of interferon-α (IFN- α) and costimulatory cytokines including CD40L (p. 1508, 1st paragraph, p. 1509. col. 2. paragraph 2 and Fig. 4c) in plasmocytoid dentritic cells (PDCs) and myeloid DCs (MDCs), which are critical to immune responses due to infection. It is stated (p. 1511, 1st paragraph) that, "Thus, both PDCs and MDCs can augment their Th1 cell supporting ability in response to TLR-7 ligands through distinct cytokines." Both TLR-7 ligands had "discernible immunostimulatory effects" on both human PDCs and MDCs (p. 1511, col. 2, 3rd full paragraph). While Ito et al. teach that CD40L constimulates an immune response with TLR-7 activation, they do not teach a composition comprising a CD40 agonist in combination with one of the TLR-7 agonists used.

Hemmi et al. teach imiquimod and R-848 have potent anti-viral and anti-tumor properties and activate cells through TLR-7 (p. 197, col. 1, paragraphs 2-3). It is also taught that TLRs recognize all microbial components in vaccine adjuvants and that these chemical ligands have similar properties to the vaccine adjuvants (p. 199, col. 2, end of 2nd full paragraph).

Melief et al. teach therapeutic anticancer vaccines. They also teach that an agonistic monoclonal antibody against CD40 turned a preventative vaccine against human papilloma virus 16 into a therapeutic vaccine in mice and in some cases, administration of CD40 alone was sufficient to completely eradicate tumors (p. 178, col. 2, 2nd paragraph). Finally,

> "It is now possible to design entirely synthetic vaccines that provide both the proper antigenic and accessory signals for induction of full scale CTL [cytolytic T-lymphocyte] effector burst as well as CTL memory. These signals employ molecularly defined innate immunity receptors such as those belonging to the TLR family, and/or adaptive immunity receptors such as CD40 or Fc receptors (*Table 1*). In cancer, it is precisely the triggering of these receptors that is lacking.... Provision of the proper TLR ligands from the microbial realm will drastically enhance these abortive responses and turn them into strong tumoricidal effector responses capable of eradicating established cancers. Both for preclinical research and for preparation and application of clinical grade vaccines, entirely synthetic formulations offer marked advantages. Rather than rely on poorly defined immune system triggers, such as recombinant vectors and adjutants

> without molecularly defined function, the novel generation of TLR ligand-mimicking adjuvants induces very precise signal transduction pathways in professional APC [antigen-presenting cell] that, moreover, can be further manipulated for desired effect by very precise changes in the ligands."

It would have been obvious at the time the invention was made to have and use a composition comprising an TLR7 agonist, such as imiquimod or R-848, in combination with a CD40 agonist, including an anti-CD40 agonist antibody, in order to increase a subject's immune response to an antigen, as well as to induce an immune response to an antigen when in the form of a vaccine. The composition and vaccine would have been obvious because Ito et al. teach TLR7 agonists are immunostimulatory and that CD40 is costimulatory. Hemmi et al. teach TLR7 agonists have potent anti-viral and anti-tumor properties and the agonists have similar properties to microbial vaccine adjuvants. Further, Melief et al. showed the use of a CD40 agonist antibody enhanced activity of a viral vaccine. Melief et al. also said that synthetic TLR ligands are very useful in vaccines, allowing for induction of "very precise signal transduction pathways", and in combination with a CD40 agonist should provide a means for destroying established cancers. Therefore, with the teachings of the synthetic TLR7 agonists and their use in immune stimulation in combination with the stimulatory effects of CD40 agonists, it would have been obvious to have either a composition comprising the two types of agonists or a vaccine comprising the agonists in the presence of an antigen, such as a tumor antigen, for the anti-viral and anti-tumor therapeutic effects discussed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

September 11, 2006